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CONTACT DERMATITIS FROM NEOMYCIN.

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AMONG the antibiotics suitable for surface application on the skin, the tetracyclines are regarded as having the lowest skin sensitization index, and neomycin has in the past been thought equal to them in this respect. As a result, the possibility of neomycin sensitivity is not commonly considered. During the past six months, however, we have seen fourteen patients with evidence of allergic sensitization to this drug. Neomycin is now prescribed extensively and its usefulness as a topical antibiotic is widely recognized, its chief advantage being that it is not usually administered parenterally or orally. Although one would not recommend its exclusion as a topical application because of the occasional development of skin sensitivity, it is essential to be aware of the possibility, particularly because of the special difficulties encountered in skin testing with neomycin.

CHEMISTRY.

Neomycin was isolated by Waksman and Lechevalier (1949) from a soil organism, *Streptomyces fradiae*. The antibacterial substances elaborated by *S. fradiae* form a mixture which contains an antifungal substance, fradecin ($C_{30}H_{34}N_4O_4$) in addition to a "neomycin complex" which has antibacterial but no antifungal properties. The neomycin complex consists of three compo-

nents (Jawetz, 1956) neomycin A, B and C, which are present in varying proportions in different preparations of the drug. Neomycin sulphate, as supplied commercially, is largely a salt of neomycin B with a small amount of neomycin C sulphate. B and C are hexa-amino compounds consisting of neamine, a pentose and a diaminohexose.

In view of the similarity in antimicrobial activity, pharmacological properties and toxic effects between neomycin and streptomycin, it is of interest that streptomycin also contains a diaminopolyhydroxycyclohexane, namely streptidine (Jawetz, 1956). This is of obvious importance in considerations of cross-sensitivity which are mentioned below.

USES OF NEOMYCIN.

Oral neomycin has recently been advocated in the treatment of hepatic coma where it has been shown to produce an early fall in the blood ammonium levels (Dawson *et al.*, 1957). The parenteral use of neomycin is limited by its toxicity; the most outstanding toxic effects in man are a sudden onset of permanent deafness and some impairment of renal function. Some of the effects closely resemble those of streptomycin.

The wide antibacterial spectrum of neomycin and the fact that it is relatively non-irritating and not highly sensitizing, make it eminently suitable for topical application. In addition, the risk of producing resistant strains is of less importance than it is in the case of other antibiotics and chemotherapeutic agents, which are more often given systemically. Bacteria rendered resistant to neomycin by repeated subculture in the presence of this antibiotic are quite regularly more resistant to streptomycin than the original strain (Gocke and Finland, 1951). Such cross-resistance is more effectively induced by neomycin than by streptomycin (Gezon and Fasan, 1951).

Neomycin is only poorly absorbed by the skin. After topical administration of not more than 0.5 gm. to the skin or mucous membranes, very little, if any, neomycin is absorbed and none can be demonstrated in body fluids or urine (Jawetz, 1956).

Some of the more common topical preparations containing neomycin are listed below. New combinations containing this drug are continually appearing on the market and the list is by no means complete. The concentration of neomycin in each is 0.5% except for Graneodin (Squibb) which contains 0.25%.

1. *Preparations Containing Neomycin Only.*

Myciguent ointment (Upjohn's of England Ltd.).

Myciguent lotion (Upjohn's of England Ltd.).

Mycifradin—for injection and external application (Upjohn's).

Neomycin ointment (Boots Pure Drug Co. Ltd.).

2. *Neomycin Combined with Another Antibiotic.*

Cicatrín ointment and powder—neomycin sulph. + bacitracin + *dl*-theonine + *l*-cystine + glycine (Calmic Ltd.).

Graneodin—neomycin + gramicidin (E. R. Squibb & Sons).

Neobacrin—neomycin + bacitracin (Glaxo Laboratories Ltd.).

Polybactrin—neomycin sulph., bacitracin, polymyxin B (Calmic Ltd.).

3. *Neomycin Combined with a Steroid.*

Cortril with neomycin (Pfizer).

Ef-Cortelan with neomycin ointment (Glaxo).

Ef-Cortelan with neomycin lotion (Glaxo).

Hydeltracin—prednisolone + neomycin sulphate (Merck Sharp and Dohme).

Hydrodeltalone with Neomycin—prednisolone + neomycin sulphate (Ward, Cassenne Ltd.).

Hydromycin—hydrocortisone + neomycin sulphate (Boots).

Hydroptic ophthalmic suspension (Merck Sharp and Dohme).

Hydrospray—hydrocortisone + neomycin + propradin (for vasomotor rhinitis, Merck Sharp and Dohme).

Neo-Cortef—neomycin + hydrocortisone (Upjohn).

Predsol-*n*—prednisolone + neomycin (Glaxo).

4. *Neomycin Combined with a Steroid and Other Antibiotics.*

Cortisporin—polymyxin, bacitracin, neomycin and hydrocortisone (Burroughs Wellcome).

Florinef with Graneodin—0.25% neomycin (Squibb & Sons).

Hydroderm—neomycin, bacitracin and hydrocortisone (Boots).

LITERATURE.

The first single cases of allergic sensitivity to neomycin were reported by Kile *et al.* (1952) and by Baer and Ludwig (1952). Sulzberger and Baer (1955) also mention that neomycin occasionally causes allergic eczematous sensitization. Epstein (1956) reported nine cases of contact dermatitis from neomycin and concluded that the sensitivity was not epidermal, but based on dermal delayed (tuberculin-type) sensitivity. The number of his cases later rose to 25 (Epstein, 1956). According to Sidi *et al.* (1957) neomycin sensitivity is rare. They found that the patients also reacted to streptomycin, and claimed that patch tests with neomycin in streptomycin sensitive patients give positive results. The cross-sensitivity is explained by the similarity of the chemical structure of these two antibiotics. Pirilä and Wallenius (1957) reported 28 cases of eczematous sensitization to neomycin and bacitracin. They believe

that neomycin sensitivity is of the usual epidermal type and they disagree with Epstein's view of a dermal-delayed type of sensitivity. Pirilä and Wallenius found no streptomycin sensitivity in their neomycin sensitive patients. They were unable to express any views on the converse issue, as they had no streptomycin sensitive patients at their disposal for testing with neomycin. Eighteen of their neomycin sensitive patients reacted to bacitracin in addition.

We are not aware of any published reports of neomycin sensitivity in this country. Two of our patients with this condition have been shown at recent dermatological meetings (Calnan and Sarkany, 1958*a*, 1958*b*) and are included in this series.

CASE REPORTS.

Case 1.—A 12-year-old boy was seen in October 1956 with impetigo of the face and scalp. He was a known case of atopic dermatitis. Graneodin ointment applied to the impetiginous areas produced a severe flare-up. Patch-testing to Graneodin ointment at that time was negative. An intradermal test with a 1% neomycin solution in November 1957 was strongly positive. Patch-testing was therefore repeated on this occasion with Graneodin and neomycin ointments, but these tests were negative; however, a 3% concentration of neomycin gave a weakly positive reaction, and 5% neomycin a distinct and typical eczematous response.

Case 2.—A 31-year-old taxi driver had suffered from seborrhoeic dermatitis for 3 months. The right retro-auricular fold became infected and this was treated by his general practitioner with Graneodin ointment. After initial improvement, an exacerbation with cracking and weeping took place with spread to the other side. Gradual improvement followed when the ointment was discontinued.

A patch test with Graneodin ointment was negative at 48 hours, and weakly positive after 96 hours. An intradermal test with 1% neomycin solution was strongly positive and produced also a focal reaction plus an increase in the erythema and scaling of both ear lobes.

Case 3.—A man aged 50, a tea porter. He scratched his right ankle on a trolley in October 1957. This became infected and he was treated with oral penicillin and Efcortelan skin lotion with neomycin applied locally. The condition worsened and when seen at hospital the right foot was markedly oedematous and showed a scaly, erythematous rash.

Patch tests with neomycin ointment and lotion were negative, but the intradermal test gave a strongly positive result.

Case 4.—A female nurse aged 38, with one year's history of otitis externa. Following treatment with Neocortef there was exacerbation and spread to both eyelids. Both patch and intradermal tests to neomycin were positive.

Case 5.—A housewife aged 65 with three months' history of a lichenified dermatitis of the neck, for which no precise cause could be found. When treated with Cortisporin by her general practitioner, the condition became worse and spread.

An intradermal test with neomycin was positive. Patch tests with Cortisporin and neomycin ointments were negative. A delayed positive reaction to patch tests with 3% and 5% neomycin was recorded after 4 days and persisted for three weeks.

She also showed a positive patch test to streptomycin, although there was no history of contact with this drug in the past.

Case 6.—A housewife aged 35 gave one year's history of lipstick cheilitis and associated dermatitis of the face. She was treated with Neocortef which at first produced an improvement, but a relapse followed soon after. She had a positive patch test to neomycin and reacted strongly to the intradermal test.

Case 7.—A housewife aged 75, with chronic eczema of the hands and feet. Fissuring of the skin of the palms with secondary infection was controlled by regular use of Neocortef ointment for six months. She then suddenly developed irritation followed by an exudative dermatitis. Patch and intradermal tests to neomycin were positive.

Case 8.—A woman aged 56, a photographic retoucher, suffered from seborrhoeic dermatitis and intertrigo. The use of Neocortef was followed by an increase in severity. Patch tests were all negative, except for a weak delayed reaction to a 5% neomycin and a strong positive to streptomycin. The intradermal test with neomycin was strongly positive.

Neomycin ointment rubbed twice daily for one week into two separate areas of normal skin produced only a minimal roughness in these two areas, but there was a focal reaction causing some exacerbation. She did not apply any of the ointment to the ear itself, but we could not exclude finger contamination. Later, application of neomycin to the right ear itself for two days caused a further exacerbation.

Case 9.—An electrician aged 39 was seen with three months' history of eczema of the right hand. During treatment with a combination of hydrocortisone and neomycin, he found the condition became worse and spread to the other hand.

Patch tests were negative; an intradermal test with neomycin was positive. When he was subjected to a "usage test" on a normal part of the skin, he showed a focal reaction with relapse of the dermatitis of the right hand.

Case 10.—A clerk aged 41, with a history of chronic rheumatoid arthritis, developed seborrhoeic dermatitis of the face and arms. When treated with Graneodin, his condition improved at first, but relapsed a fortnight later.

Patch tests with Graneodin and neomycin ointments were negative, the test with 5% neomycin ointment was weakly positive and the intradermal test gave a positive result.

Case 11.—A tailoress aged 40 suffered from nickel dermatitis. When the lesions on her ear lobes were treated with a combination of hydrocortisone and neomycin there was initial improvement, followed by an exacerbation and spread of the dermatitis to the eyelids. Patch and intradermal tests to neomycin were positive.

Case 12.—A housewife aged 66 was treated with Graneodin ointment for angular stomatitis. She developed a dermatitis of the face and when tested showed a delayed positive reaction to Graneodin. The intradermal test with neomycin was also positive.

Case 13.—A female clerk aged 39 was treated with an ophthalmic suspension of neomycin for an affection of the eyes. Later, she used Neocortef for an associated dermatitis of the eyelids and the condition became worse.

Patch and intradermal tests to neomycin were positive.

Case 14.—A retired man aged 67 was seen with six years' history of seborrhoeic dermatitis. He was treated with a number of ointments by his private doctor and several dermatologists.

When he was seen at hospital with an exacerbation affecting mainly his face, patch tests with various likely sensitizers were carried out. Sensitivity to neomycin was found. It was subsequently discovered, through the patient's general practitioner that ophthalmic neomycin had, in fact, been prescribed for blepharitis on a previous occasion.

Among these patients we discern no predisposition as regards age or sex. The primary dermatosis was always one in which the skin surface is breached by trauma or infection, or shows some degree of eczematous change.

SKIN TESTING.

Patch tests with neomycin and the neomycin-containing preparation in question were carried out on the skin of the back. The results were read after

48 hours and again after 96 hours, and in a few cases also later. In relevant cases, we examined for sensitivity to hydrocortisone ointment. Seven patients (Cases 1, 8, 10, 11, 12, 13, 14) were tested to the ointment base, with negative results in all.

In the early stages of this investigation, negative patch tests or an occasional delayed positive result were the rule, while the intradermal test was strongly positive in each case. At that time, routine testing was carried out with Graneodin ointment in which the concentration of neomycin is 0.25% and also a neomycin ointment containing 0.5% of neomycin sulphate. Poor absorption of neomycin by the unbroken skin seemed to be a possible explanation for the negative results and we therefore began to use, in addition, higher concentrations, i.e. 3% and 5% neomycin sulphate in soft paraffin. Eleven of the patients were tested to streptomycin and eleven to bacitracin. Four patients were tested to framycetin.

The intradermal tests were performed on the flexor aspect of the forearm; 0.05 ml. of a 5% solution of Mycifradin (neomycin sulphate) was used in the early stages and 0.05 ml. of a 1% solution during the remaining period. The reactions were examined after 48 hours, again after 96 hours and in some cases also later. A raised erythema more than 0.5 cm. in diameter was considered positive. All the patients in this series were positive to the intradermal test.

Twelve other patients with other skin conditions (dermatitis of endogenous and exogenous origin or psoriasis) who had not used neomycin, served as controls for the intradermal injections. In six of these 0.05 ml. of a 5% solution of neomycin sulphate was used and the 1% solution in the remainder. None showed any reaction. Twenty-eight other patients, suspected of having developed neomycin sensitivity on clinical grounds, were tested with the intradermal and patch tests, but the results were all negative. Of these, two presented some difficulty. The first was a 59-year-old man with seborrhoeic dermatitis who noticed exacerbation of his dermatitis when he was treated with Graneodin ointment eighteen months previously. Patch tests were negative. The intradermal test produced a purplish discoloration 4-5 mm. in diameter which was not visibly raised above the surface of the skin. A similar appearance was found when the test was repeated. The patient was then advised to rub the ointment into two separate areas of normal skin on the arm twice daily for one week. This produced no abnormality. He was then instructed to apply the ointment to his retro-auricular fold which was the site of a mild dermatitis. This again produced no ill effects. We concluded that the peculiar reaction to the intradermal test was a false positive and that he was not allergic to neomycin.

This doubtful reaction to an intradermal test was also seen in a second patient, a man of 41, suffering from allergic vasculitis. Neomycin applied to an ulcer on his leg appeared to cause an exacerbation. Patch tests were negative. The intradermal test gave the same type of reaction with some necrosis in the

centre. In view of the presence of the purpuric state, it was not considered indicative of neomycin sensitivity. A usage test carried out on the lines mentioned was also negative. In several other patients in whom all the tests were negative, the suspected ointment was again used without untoward effects.

Table I shows the patch-test results with the various neomycin containing preparations used. Not all the patients were tested to each one of them.

TABLE I.—*Results of Patch Tests.*

Case No.	Graneodin (0.25%).		Ung. neomycin (0.5%).		Neomycin 3% Paraff. moll.		Neomycin 5% Aq.		Neomycin 5% Paraff. moll.	
	48 hrs.	96 hrs.	48 hrs.	96 hrs.	48 hrs.	96 hrs.	48 hrs.	96 hrs.	48 hrs.	96 hrs.
1	.	—	.	—	.	—	.	—	.	—
2	.	—	.	+	.	..	.	..	.	..
3	.	..	.	—	.	..	.	—	.	..
4	.	..	.	+	.	..	.	+	.	..
5	.	..	.	—	.	—	.	±	.	—
6	.	..	.	±	.	..	.	±	.	..
7	.	—	.	±	.	+	.	+	.	+
8	.	..	.	—	.	—	.	—	.	±
9	.	—	.	—	.	—	.	—	.	—
10	.	—	.	—	.	—	.	..	.	±
11	.	..	.	..	.	..	.	..	.	±
12	.	—	.	—	.	±	.	..	.	—
13	.	—	.	+	.	..	.	..	.	+
14	.	—	.	±	.	..	.	..	.	+

In Table II are recorded the results of intradermal testing, and of patch-testing with substances other than neomycin. We were unable to confirm any associated sensitivity to bacitracin as found by Pirilä and Wallenius (1957) in six patients. It should be mentioned that pure bacitracin was not available to us and we used the 5.5 unit discs supplied for testing antibiotic sensitivity of bacteria on agar plates. Two cases cross-reacted to streptomycin 1%, while nine others did not.

TABLE II.—*Results of Intradermal Tests and Patch Tests to Other Substances.*

Case No.	Intradermal neomycin 0.05 ml. of 1% soln.	Patch tests.			
		Neomycin base.	Bacitracin 5.5 units.	Streptomycin 1%.	Framycetin 1.5%.
1	.	+++	.	—	..
2	.	++	.	—	..
3	.	+	.	..	..
4	.	++	.	..	..
5	.	+	.	—	..
6	.	++	.	..	..
7	.	++	.	—	..
8	.	+++	.	—	..
9	.	+	.	—	..
10	.	+	.	—	—
11	.	+	.	—	..
12	.	+	.	—	—
13	.	+	.	—	—
14	.	+	.	—	—

Seven streptomycin sensitive patients were patch-tested to various concentrations of bacitracin, and intradermally tested with neomycin. No positive results were obtained. None of four patients reacted on patch test to framycetin 1.5%, the active agent in Soframycin (Roussel Ltd.).

HISTOLOGY.

A positive reaction produced by an intradermal test with 0.05 ml. of 1% neomycin was biopsied after 48 hours in Case 2. The section shows (Fig. 1) a round-cell infiltrate enveloping the vessels and appendages. In the epidermis,

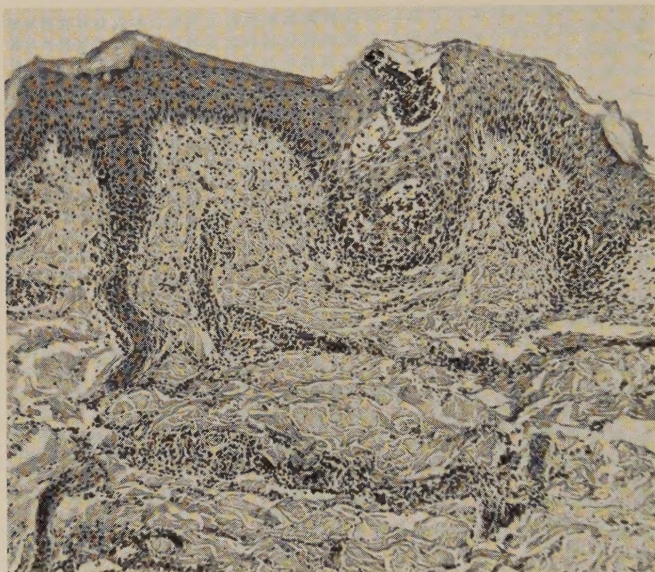


FIG. 1.

there is acanthosis with spongiosis and a few vesicles. The appearances are those of eczema.

Another positive intradermal reaction (Case 4) shows only slight spongiosis and a more intense round-cell infiltration of the corium, mainly around the vessels and appendages.

For comparison, the positive patch-test reaction in Case 4 was biopsied (Fig. 2). There is a perivascular round-cell infiltration with acanthosis and spongiosis in the epidermis. Although the intradermal test of Case 4 shows changes principally in the dermis compared to the more prominent epidermal changes in the patch-test site, both reactions are essentially similar.

Epstein (1956) states that microscopic examination of intradermal tests

with neomycin shows purely dermal reactions in the first 48 hours, and may reveal epidermal changes later.

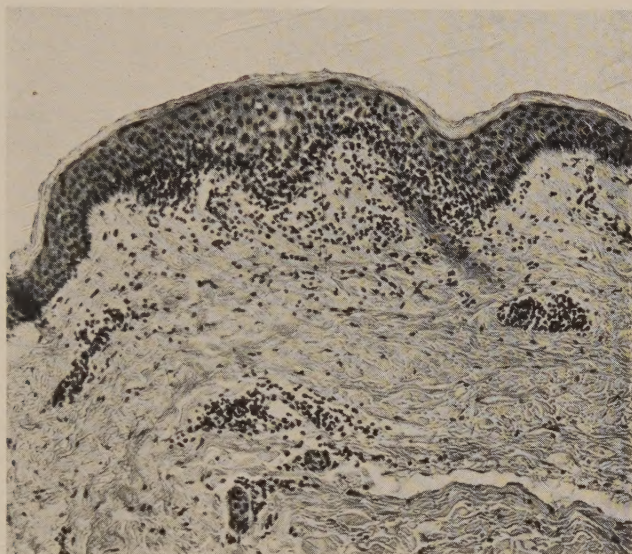


FIG. 2.

DISCUSSION.

Contact dermatitis from neomycin may easily be missed. Epstein (1956) suggests three possible reasons: First, dermatitis from neomycin may be superimposed on a pre-existing eczematous reaction; second, patch tests are often negative; and third, preparations containing a combination of neomycin and hydrocortisone may appear temporarily beneficial because the hydrocortisone suppresses the inflammation caused by the neomycin.

Positive intradermal tests confirmed the diagnosis in all our patients. Patch-testing with neomycin in the concentration found in various proprietary preparations was often negative, but higher concentrations gave positive reactions more frequently. Only one patient with a relatively weak intradermal reaction (Case 9) failed to react to a patch test with 5% neomycin. Several others reacted very weakly at this strength. Poor absorption of the drug by the intact skin appears to us to be sufficient to explain the more reliable results obtained by intradermal testing.

Cross-sensitivity to streptomycin was recorded twice in this series, a possibility first noted by Sidi *et al.* (1957). It is probably due to the close chemical relationship of neomycin A and streptidin, a component of streptomycin. Both are derivatives of aminohydroxycyclohexane (Jawetz, 1956). On the

other hand, none of seven streptomycin sensitive patients cross-reacted to neomycin. There is no reason to doubt that it may happen, as stated by Sidi *et al.* (1957); but cross-sensitivity reactions are complex and depend on concentrations and the nature of the primary and secondary allergens, in addition to the specific reacting chemical groups. We found no cross-sensitivity to framycetin in four neomycin sensitive patients.

The appearances of the positive neomycin patch tests did not differ from the characteristic eczematous response found with other allergens. Epstein (1956), when he first drew attention to the difficulties of skin-testing with this substance, suggested that the occasional or inconstantly positive reactions were an expression of dermal delayed tuberculin-type sensitivity, rather than epidermal sensitivity; and that his histological findings supported his opinion. We question this distinction, since allergic contact dermatitis is not synonymous with epidermal sensitivity; both the dermis and epidermis take part in this reaction, though there is considerable argument as to which is primarily affected. The proportion of the dermal element (vascular dilatation and oedema) to the epidermal (vesiculation) varies enormously from case to case. A patch test can be strongly positive when the same allergen introduced intra-cutaneously produces no reaction. The converse is also true (Goldsmith and Hellier, 1954). Rokstad (1946) had the same experience with turpentine dermatitis. There is no immunological difference between the two types of reaction.

Our conclusion, therefore, is that the anomalous patch-test results are due to slow absorption of neomycin by the skin. Various agents such as lauryl sulphate, propylene glycol, and soap solutions can be used to aid penetration. We have not employed any of them because they may give false reactions from damage to the skin surface which cannot be excluded entirely by the use of control tests.

SUMMARY.

Fourteen cases of contact dermatitis from neomycin are described. Negative patch tests are frequent, but intradermal tests are always positive.

This sensitivity is not rare and is of the usual eczematous type. Clinical, histological and patch-test evidence is presented. The negative patch tests are due to failure of penetration of the allergen.

Cross-sensitivity with streptomycin has been observed, but no neomycin sensitivity was found in the streptomycin sensitive patients tested.

There was no evidence of an associated sensitivity reaction to bacitracin or framycetin.

This study was made possible by many members of the staff of St. John's Hospital for Diseases of the Skin and of the Institute of Dermatology, who have allowed us to investigate their patients. We are grateful to all of them. Dr. H. Haber has given us help with the histology, and Mr. R. J. Lunnon is responsible for the photomicrographs.

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LEIOMYOMA CUTIS.

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LEIOMYOMATA of the skin were classified by Besnier (1880) as solitary or multiple. The former occurred in the dartoid zones, especially the perianogenital and axillary regions and the nipple. Multiple lesions might occur anywhere.

Babes's (1884) classification was based on anatomical and pathological data, as follows :

- (i) Leiomyoma derived from the smooth muscle of blood vessels.
- (ii) Those derived from the muscoli arrectores pilorum, sometimes in naevi.
- (iii) Those derived from the smooth muscle layer of the "*zones dartoïques*". Babes included in this group the more diffuse lesions which occur on the genitalia and legs in combination with lymphangiectasia and Bazin's pachydermia myxomatodes.
- (iv) Those derived from the smooth muscle of deeper tissues or from embryonic displacements ("*versprengte Keime*"). Branchogenic leiomyoma belongs here.

Other types have subsequently been added to this classification, such as those supposedly originating from the smooth muscle of sweat glands, those from the superior tarsal muscle and a number of mixed types.

Leiomyoma of the skin may occur at any age. Some familial, hereditary cases have been observed. According to Stout (1937), multiple lesions occur twice as often in men as in women, but solitary tumours occur equally often in the two sexes. They vary in size from a pin-point to that of a man's head and in hue from skin-coloured to reddish-brown. They grow slowly and small tumours may disappear spontaneously. They may therefore be difficult to diagnose, particularly if the typical pain is absent. This pain is described as stabbing, pinching, burning or griping and it is usually limited to the tumour. Sometimes it radiates and it may be paroxysmal. It may arise spontaneously or be provoked by varied circumstances, e.g., emotional stress, fatigue, cold, menstruation or pregnancy, or by pressure, especially when manipulated. It is believed that contraction of the tumour gives rise to pain through ischaemia, or by pressure or traction on nerves.

Grzybowski (1933) demonstrated neurofibrils in leiomyomata by silver impregnation and he believed them to be responsible for the symptoms. The same opinion was held by Halter and Hornemann (1952). Some authors have suggested a relationship between vascular leiomyomata and the likewise painful

glomus tumours (Peyri, 1943; Ekeström, 1950). An angioleiomyomatous glomus tumour was described by Vilanova and Grau-Barbera (1944). It must be noted, however, that neither Ekeström nor Saunders and Fitzpatrick (1956) succeeded in demonstrating neurofibrils in vascular leiomyomata. In the 13 cases we investigated in 1951, we did not observe an abnormal amount of nerve tissue in material prepared by Bielschowski's silver impregnation technique. On the contrary, we gained the impression that leiomyomata were poorly provided with nerves. Ormea (1951), using the same method, noted hypertrophy and degeneration of nerve tissue. He reported swollen neurofibrils in serpiginous arrangement, with dilatations and changes in the terminal network. These accompanied changes in smooth muscle, viz., homogenisation and degeneration of nuclei. He felt that the changes in muscle and nerve were simultaneous. Nödl (1953) found more or less similar microscopical changes, but formed a different opinion. He believed that primary importance had to be attributed to the hypertrophy of the terminal network. He pointed out that changes in nerve tissue could be found where no changes in muscle could be observed. He believed that multiple leiomyomata were to be looked upon as a neurocutaneous syndrome.

Leiomyoma derived from hair muscle is the commonest form in the skin (50%, according to Sutton, 1912). The favourite sites are the hairy parts of the body, especially the cheeks. As a rule there are multiple, spherical tumours, 1 to 6 mm. in diameter. Sometimes they occur in naevi: Jesionek and Werner (1907) described such a case as "naevus verrucosus pigmentosus", to which the adjective "leiomyomatosus" might justifiably have been added.

The diagnosis of hair-muscle leiomyoma can be made with certainty only if it can be demonstrated that the muscle fibres of the arrectores pilorum fuse with the myoma. Hair-muscle leiomyomata are seated in the dermis and the papillary layer is not involved. They are not encapsulated. Sometimes the muscle fibres, which run in bundles in every direction, appear to invade the surrounding connective tissue (pseudoinfiltrative growth) but real signs of malignancy and significant cellular infiltration are nowhere to be seen. Small nests of lymphocytes may be found at the border of the lesion. When they increase in size, these tumours show decrease in collagen at the centre. Nearly all the elastic fibres disappear and are seen only in the broader collagenous septa which separate the smooth-muscle bundles. All types of leiomyoma of the skin may show foci of degeneration as do uterine leiomyomata. The nuclei of the muscle cells in the different kinds of leiomyoma are usually normal; they may be short or broad and are sometimes curved. Giant nuclei, nuclear disintegration and multinucleate forms of muscle cells have been described. Cytological atypicality is uncommon and malignant degeneration extremely rare.

Leiomyomata derived from deeper tissues and from embryonic rests do not belong to the group of autochthonous skin leiomyomata. They may be derived,

for instance, from the puborectal aponeurosis, the rectovaginal septum or the prostate gland. They are surrounded by firm fibrous capsules and may attain a considerable size.

Sobotka (1908) pointed out that smooth muscle fibres unconnected with hair follicles may be present at the junction of the cutis and subcutis around the umbilicus, on the forehead and cheeks, near the ears, on the back and on the extensor surfaces of the thighs. It is therefore difficult to judge whether a given leiomyoma originated from "embryonic rests". As a rule, these leiomyomata are located deeper than the hair-muscle tumours, but sometimes it is impossible to differentiate them.

For a discussion of other leiomyomata of the skin, we refer the reader to a previous article by Jansen (1952).

Numerous cases of cutaneous leiomyoma have been reported. The description of another might seem superfluous but for the extraordinary extent and appearance of the tumours in our case.

CASE REPORT.

History.—A Dutchman aged 26 years had suffered from a skin disease since he was 14, when tiny nodules appeared in the skin of the right shin. The elements increased in size and number and he felt severe pain which disabled him in his work as a farmer and obliged him to seek medical advice. During the past five years in particular, many fresh lumps had appeared, the older ones had increased in size at a greater rate and had become more painful. Pain was elicited by pressure and knocks, by cold and by sudden change from cold to warmth. The slightest touch, even the contact of his trousers, induced paroxysms of excruciating pain. He described the pain as resembling toothache. Pressure or knocks gave rise to stabbing pain as if the tumours were being pricked with needles. Severe spontaneous pain might occur when he became excited or angry. In addition to pain, he sometimes perceived itching and a feeling as though the leg were enveloped in an elastic bandage. This happened particularly when changing from cold to warmth. In bad weather, he suffered most from pain and itching; in good weather he had little discomfort. These features were so outstanding that he claimed to be able to foretell changes in the weather by means of the sensations in his leg. He also noticed that in cold weather, the tumours were firmer. After injury, two tumours on the shin had bled but gradually healed. He felt well otherwise.

Family History.—A paternal aunt had an itching, painful nodule near the left elbow.

Examination.—Except for the skin, no important abnormality appeared to exist. The hard palate was higher than normal, the little fingers slightly curved. He had slight bilateral pes cavus and acrocyanosis of hands and feet. Blood and urine normal. Blood W.R. negative, Mantoux test 1,1000 negative, B.M.R. + 20%. General internal examination and skiagrams of the chest and long bones normal.

The eruption was present on the anterior and lateral aspects of the distal third of the right thigh and the proximal two-thirds of the right leg, mainly pretibially, extending medially and laterally as far as the calf. It was composed of numerous globular or ovoid tumours 1 mm. to 4 cm. in diameter (Fig. 1). The largest were on the front of the shin and were so closely set that they merged. Slight elevations were present on the surface of the larger tumours. The smaller elements varied in

colour from a vivid red to dull purple. The larger tumours showed a taut, shining surface of milky, bluish-gray hue with tortuous telangiectases. Some showed one or more hairs, but on the whole they did not seem to be connected with follicles. A few small lenticular elements were present at some distance from the main eruption on the right thigh and leg. A similar lesion was situated on the extensor surface of the left upper arm.



FIG. 1.

If one tried to handle the nodules, the patient at once assumed a defensive and fugitive attitude, shielding the eruption with his hands, though he yielded after persuasion. Careful palpation revealed that the tumours were firm and elastic. They were attached to the dermis but were to some extent mobile over the subcutaneous tissue. Palpation of most elements was extremely painful, particularly of the larger tumours. Small painless lymph glands were present in the axillae and groins. There was some folliculitis of the neck, shoulders and the extensor side of the left thigh and he had seborrhoeic alopecia.

Investigation.—Adrenaline 0.1 mgm. in 0.1 ml. was injected into two of the larger tumours. Their colour faded at once and they became harder. The prick of the needle and the injection of the fluid caused little immediate pain, but after a minute or two, severe pain occurred in the tumours injected and the painfulness of the other

lesions also increased. The effects of the injection were still evident after $2\frac{1}{2}$ hours and took 4 hours to disappear. Physiological saline injected in the same way elicited only slight discomfort.

The origin of the tumours was puzzling. If we were to assume that they originated from embryonic rests, we had to exclude that they sprang from smooth muscle normally present in the skin of these areas. We succeeded in solving this problem by studying serial sections of the smallest elements with a diameter of only 1 to 2 mm. Haematoxylin and eosin, van Gieson and Weigert stains, Masson's trichrome and Bodian's silver impregnation were used.

The epidermis covering the larger lesions is flattened but otherwise normal (Fig. 2). No smooth muscle is found in the papillary layer. The rest of the dermis is markedly

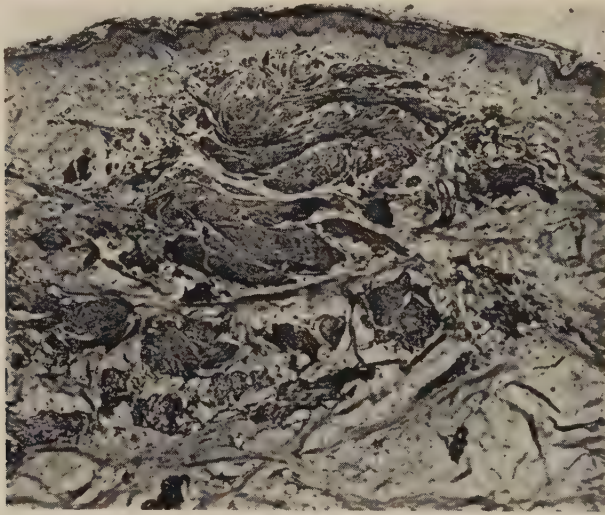


FIG. 2.

thickened and filled with smooth muscle tissue. At some parts at the periphery, smooth muscle bundles of varied diameter are interwoven and separated by connective tissue. Towards the centre, the density of the muscle tissue increases and less connective tissue is seen between the bundles. The centre is composed of a dense mass of smooth muscle and only a few collagen fibres remain. The smooth muscle fibres appear essentially normal. Elastic fibres are practically absent from the papillary layer overlying the tumour. In the tumour itself, elastic fibres are present only in the broader connective tissue septa between the muscle bundles.

Many capillaries are visible in the myomatous tissue and small arterioles and veins are seen at the border of the tumour. As a result of its expansive growth, the tumour has left only a narrow band of connective tissue at its lower border, separating it from the hypoderm. It therefore appears to have a fibrous wall, but it is not genuinely encapsulated. Skin appendages are absent between the muscle bundles; here and there at the border, numerous sweat glands are found as though pushed aside by the tumour, and there is some lymphocytic infiltration.

It is clear that the smaller the tumour, the less the bundles of smooth muscle are compressed. Serial sections of some of the smallest elements reveal that the latter are all derived from hair muscle. Hypertrophic hair muscle branches into a number of smooth muscle bundles which grow outwards into the otherwise normal dermis.

The smooth muscle tissue gradually increases and pushes aside the epidermal appendages until, finally, the original connection with the follicle is lost. The tumour, which at first is composed of separate bundles, pushes aside the collagen and elastic tissue of the dermis and grows into a compact mass of smooth muscle, which lifts up the epidermis and expands down to the junction of dermis and hypoderm.

After silver impregnation (Bodian) a number of nerve fibres can be observed in the tumours. They resemble those seen in normal smooth muscle such as the arrectores pilorum and are neither quantitatively nor qualitatively abnormal. The papillary layer is also entirely normal in this respect.

Treatment.—The patient was treated by Dr. C. A. Honig, consulting plastic surgeon. The skin containing the tumours was excised, together with the underlying subcutaneous tissue. No invasion of the latter was found. The wound was closed with a Thiersch graft which took well and healing was uneventful. The patient was allowed to leave the surgical department four weeks after the operation. He was in good health and free of symptoms. A month later, he was seen in the outpatient department, free of pain and discomfort for the first time for many years and able to work once more as a farmer.

SUMMARY.

The diagnosis and classification of leiomyoma cutis is discussed.

A case of extensive leiomyoma of the skin is described.

Microscopic examination proved the lesions to be of hair-muscle origin but no changes were demonstrated in neural tissue in or near the myomata.

We wish to thank Professor Dr. M. T. Jansen of the Department of Histology of the University of Utrecht for help in studying the silver impregnated sections.

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A COMPARISON OF GLYCYRRHETINIC ACID AND HYDROCORTISONE OINTMENTS.

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THE anti-inflammatory action of locally applied hydrocortisone is well known, and this substance is of great value in the treatment of various dermatoses.

When liquorice extract was found to have a deoxycortone-like activity (Molhuysen *et al.*, 1950) it was hoped that its active principle, glycyrrhetinic acid (GA), might prove a cheap and effective substitute for hydrocortisone. Successful results were claimed for ointments containing GA by several writers (Colin-Jones, 1956, 1957*a*, 1957*b*; Colin-Jones and Somers, 1957; Evans, 1956; Sommerville, 1957; Pozzo, 1957). Others (Bettley, 1956; Russell, 1956; Hall and Jefferson, 1956) were unimpressed, and found no appreciable difference between ointments containing GA and the base alone.

In view of the discrepancy of these reports it was felt that there was a need for a further trial to determine whether an ointment containing GA had an anti-inflammatory effect comparable to a standard hydrocortisone ointment (Hc).

CLINICAL MATERIAL.

The following cases, selected as likely to benefit from hydrocortisone, were used in the trial:

Localized Eczema—

Hands	.	.	.	.	.	.	10
Ears and retroauricular folds	.	.	.	.	.	.	8
Scrotum	.	.	.	.	.	.	3
Face	.	.	.	.	.	.	1
Axilla	.	.	.	.	.	.	1
Thigh	.	.	.	.	.	.	1
Toe	.	.	.	.	.	.	1
<i>Discoid Eczema</i>	.	.	.	.	.	.	5
<i>Pruritus ani</i>	.	.	.	.	.	.	4
<i>Balanitis</i>	.	.	.	.	.	.	1

Six patients defaulted and twenty-nine completed the trial.

METHOD.

All patients were treated with hydrocortisone for a week and then glycyrrhetic acid for a week, or *vice versa*.

For the first week each patient received either 1% hydrocortisone ointment or 1% glycyrrhetic acid in a water-miscible base of similar composition to apply twice daily. The patient's condition was then compared both with his initial state and with the state expected had hydrocortisone or an equally effective remedy been used in his treatment. After one week the ointment was changed to GA or Hc respectively, and at the end of the second week the patient's state was again compared with the condition at the end of the first week and the anticipated state had hydrocortisone or an equivalent been used during the second week of the treatment. For example, the patient who was seventh in the series received prescription 7a for a week and prescription 7b for the second week, then either 7a or 7b depending on which proved more effective. The dispenser had a code concealed from everyone else and randomized by shuffling cards to determine the composition of *a* or *b* for each number. Finally, the patient was asked to choose the ointment which he considered better, and he continued to use this.

RESULTS.

These were recorded on a standard card (Fig. 1) and are summarized in Figs. 2-5 which allow the following comparisons :

- (i) Actual state with state at previous visit.
- (ii) Actual state with anticipated state had hydrocortisone or an equivalent been used.
- (iii) A comparison by the patient of the two different ointments.

Hydrocortisone used first.—Of the seventeen patients on whom Hc was used first, four were much better, and nine better than previously ; three were the same and one worse than before. When compared with the predicted state, two did much better, six better than anticipated, six equalled, two were below and one much below expectation.

These results may be expressed numerically by multiplying the score shown on the card by the number of patients at this score and then dividing by the total number of patients to give a mean score. This is included as a simple description of the experience of the average patient, and in view of the consistency of the results, appears to be a useful descriptive abbreviation.

The mean score for Hc was therefore

$$\frac{1}{17}[(4 \times 2) + (9 \times 1) + (3 \times 0) + (1 \times -1)] = +\frac{16}{17}$$

compared with their original state.

When compared against expectation the mean score for He was

$$\frac{1}{17}[(2 \times 2) + (6 \times 1) - (6 \times 0) + (2 \times -1) + (1 \times -2)] = +\frac{6}{17}$$

Glycyrrhetic acid used first.—Of the twelve patients on whom GA was used first, two showed great and two moderate improvement ; three were unchanged,

THERAPEUTIC TRIAL.

Case No. 29

Name *Helen SMITH* No. *8391/55* Age. *73* Sex. *F*

Date *2. XI 56*

Summary *Six months, retroauricular eczema.*
Marginal Blepharitis

Expected state next visit. (Due *9.11.56*)

About 50% improvement

Prescribe ointment 1a.

VISIT 2. Date *9.11.56* "*No change at all.*"

Present state compared to visit 1. $-2 \quad -1 \quad 0 \quad 1 \quad 2$

Comparison with expected state $-2 \quad -1 \quad 0 \quad 1 \quad 2$

Expected state next visit. (Due *16.11.56*)

About 50% improvement

Prescribe ointment 1 b.

VISIT 3. Date. *16.11.56* "*Better than with the last ointment, now dry and not itching.*"

Present state compared to visit 2 $-2 \quad -1 \quad 0 \quad 1 \quad 2$

Comparison with expected state $-4 \quad -3 \quad -2 \quad -1 \quad 0 \quad 1 \quad 2$

Prescribe whichever considered better
Record which *b*

VISIT 4. Date *23.11.56* *Still improving. "The last two ointments are better than the first."*

SCORING

2nd visit -2 much worse than expected
 -1 worse than expected
 0 as expected
 1 better than expected
 2 much better than expected

3rd visit.

As above except that

-3 worse than at visit 2, better than at visit 1
 -4 As bad as at first visit.

FIG 1.

three appeared worse and two much worse. When compared with the expected state, three did better, one was equal and eight did not do as well as anticipated.

On this basis the scores were $-\frac{1}{12}$ and $-\frac{8}{12}$ respectively.

These pairs of scores are, of course correlated.

When GA was used after Hc had been used for a week, of the fifteen remaining patients (one had been cured the previous week and two failed to co-operate in the second week of the trial), twelve had deteriorated and three showed improvement. Of the twelve who deteriorated all did worse than anticipated,

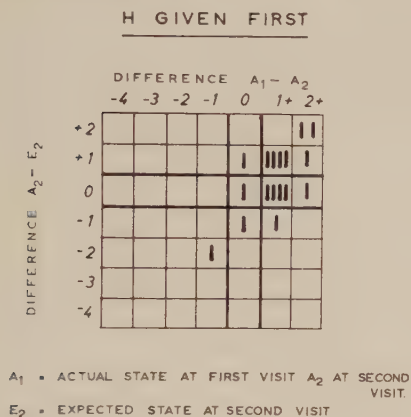


Fig: 2

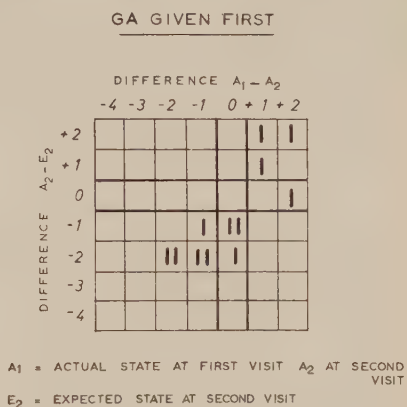


Fig: 3

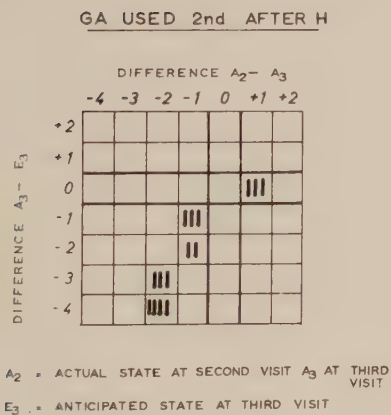


Fig: 4

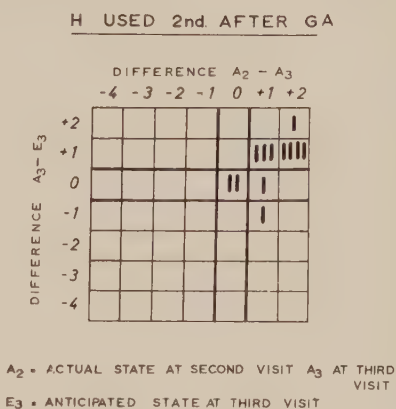


Fig: 5

while the three others reached the predicted stage. The mean scores were therefore $-\frac{16}{15}$ and $-\frac{32}{15}$ respectively.

When Hc was used after GA, ten of the twelve patients showed improvement and two no change. Of these twelve, eight were better than expected, three

were as anticipated and one was worse. The mean scores were respectively $+\frac{15}{12}$ and $+\frac{8}{12}$.

At the end of the fortnight twenty-two patients expressed a definite preference, nineteen for Hc and three for GA. The possibility was considered that GA might be superior to Hc in the treatment of one particular condition. The three patients, however, who preferred GA did not conform to any particular clinical pattern, being single cases of pruritus ani, eczema of toe and balanitis.

SUMMARY.

When GA was used the change in state was fairly equally divided between deterioration and improvement

$$\left(\text{mean score} - \frac{1}{12}\right),$$

while the outcome was consistently below that expected on the basis of past experience

$$\left(\text{mean score} - \frac{8}{12}\right);$$

this finding is even more impressive as evidence of inferiority when it is appreciated that, when Hc was used, the prognosis showed evidence of chronic pessimism. In the case of Hc the whole pattern of response is obviously different, most cases showing a marked improvement

$$\left(\text{mean score} + \frac{16}{17}\right)$$

and this improvement considerably exceeded that expected

$$\left(\text{mean score} + \frac{6}{17}\right).$$

When GA and Hc were given in the second period the superiority of Hc over GA was even more marked than in the first. The expectations then had the advantage of being founded on experience in the same patient as well as on general experience, and the results show an even more marked discrepancy between the two, no case doing better than expected on GA and only one doing worse than expected on Hc. One case had to be excluded because recovery on Hc was complete, leaving no opportunity for a trial on GA. Patients on GA not only did not improve, but most of them deteriorated and lost such ground as they had gained on Hc.

Nineteen patients expressed a definite opinion of the superiority of Hc, against three preferring GA. Those who preferred GA did not conform to any particular clinical pattern.

The consistency of these several sets of data and the extent of the difference is convincing evidence that GA is markedly inferior to Hc.

CONCLUSIONS.

When twenty-nine patients were treated with hydrocortisone and glycyrrhetic acid using a cross-over technique there was clear evidence that hydrocortisone was superior in the great majority of patients.

We are indebted to Genatosan Ltd., for samples of Genodex used in this trial.

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NORTH OF ENGLAND DERMATOLOGICAL SOCIETY.

Manchester, May 1958.

Melkersson's Syndrome.—Dr. G. AUCLAND.

A spinster aged 62 years, a weaver.

History.—Twenty-eight years ago she suddenly developed a complete left facial palsy. Partial recovery occurred but residual symptoms still persist.

About 20 years ago she began to suffer from attacks of swelling, redness and inflammation of the lower lip extending almost to the chin and associated sometimes with superficial ulceration of the mucous membrane on the inner surface of the lower lip. Gradually permanent thickening of the lip and infiltration of the soft tissues

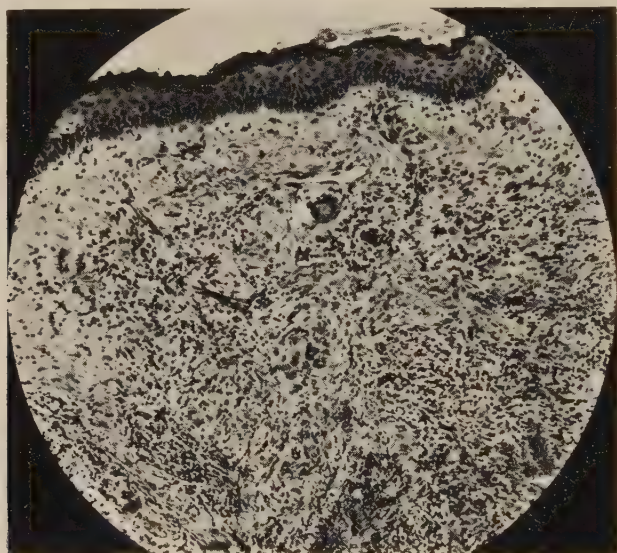


FIG. 1.

affected by the inflammation developed. The attacks subside in 3 or 4 weeks without treatment and in 1 to 2 weeks with antibiotics. Intervals between attacks vary from two months to a year.

Examination.—There is a partial left facial palsy; induration and redness of the lower lip and soft tissues extend almost to the point of the chin. The tongue is normal.

Investigations.—W.R. negative. Blood count normal.

Histology.—“Tuberculoid granulomata in the cutis. Sarcoidal arrangement with giant cells” (Fig. 1).

Comment.—The association of facial palsy with recurrent inflammatory swelling of the lip leading to stationary oedema constitutes Melkersson's Syndrome. In 25% of cases lingua plicata is also present as a congenital abnormality. The condition is probably a separate entity from cheilitis granulomatosa (Miescher) which

can be due to various causes such as focal sepsis or allergy. The histology, however, is similar.

Multiple Skin Necroses with Hypoproteinaemia. —Dr. G. AUCLAND.

A married woman aged 75 years, a retired civil servant.

History.—No relevant illness until 1955 when she developed "sores" on both upper arms which healed in 3 weeks.

In 1956 she had a similar condition and later in the year developed a large crusted ulcer below the left knee which healed only after several months.

In April 1957 further ulcers appeared on the left arm, thighs, right shin and left foot which were soon followed by persistent oedema of the feet and legs. During the subsequent 10 months fresh ulcers appeared at intervals, beginning as a small patch of erythema with a central vesicle which rapidly broke down into a necrotic area of ulceration.

The eyelids, neck, buttocks, toes, soles and legs were the sites affected. Some of the ulcers remained small but others reached a large size.

Her general health has been good except for a poor appetite during the past 4 years. There is no history of bowel upset or previous septic episodes.

Examination.—A thin intelligent woman very alert for her age. There are many scars of varying size on feet, legs, buttocks and neck, with two large ulcers not yet healed on the legs and a number of smaller ulcers on the buttocks. Minimal pitting oedema on the dorsum of the right foot.

Investigations.—(June 1957) W.R. and Kahn negative. Urine normal.

Hb 11.7 g. WBC 8000 (Neutros. 64.5%, eos. 4.5%, lymphos. 31.0%).

Blood urea 37 mgm.%. Blood culture sterile.

E.S.R. 1st hour 77 mm., 2nd hour 108 mm.

Swabs from ulcers—*B. proteus* and *Staph. aureus* (coagulase positive) both sensitive only to chloramphenicol and streptomycin.

Chest skiagram—N.A.D.

Serum proteins: Albumin 1.2%, globulin 2.4%.

Histology of edge of ulcer shows "superficial ulceration with areas of non-specific ulceration. No evidence of polyarteritis".

Liver function tests normal.

Progress and treatment.—For the first 4 months she was given a high protein diet, supplementary protein, vitamins, antibiotics, mercurial diuretics, hydrochloric acid and pepsin, and a variety of local treatments to the ulcers without benefit. Her total serum proteins varied between 3.1% and 4.8%. The albumin fluctuated between 1.2% and 2.2% and the globulins between 1.8% and 2.6%.

An electrophoretic curve in July 1957 showed a general reduction in all protein fractions with a gross reduction in the albumin fraction and a marked reduction in γ -globulin.

A second biopsy of a very early lesion before ulceration shows "Thinning of the epidermis and loss of rete pegs. There is sub-epithelial oedema with slight round-cell infiltration extending along perivascular channels".

In November 1957 prednisolone therapy was started and was followed by an immediate rise in total serum proteins to 6.0% which has never fallen since, and indeed rose to 6.3% after cessation of this treatment. The globulins rose to a maximum of 3.8% and the albumin to 3.0% although this figure was not maintained (Table I). The ulcers began to heal within 2 weeks of starting steroid therapy and the oedema of the legs also steadily diminished. After 4 months this treatment was stopped but clinical improvement continued.

In May 1958 her electrophoretic curve showed a marked increase in α_1 and α_2 globulins, and reduced albumin. At no time was albumin found in the urine.

Comment.—There seems little doubt that hypoproteinaemia was responsible for this patient's oedema and ulceration. The cause of the low serum protein is obscure ; none is being lost in the urine and despite a high protein intake for several months there was only a small rise and no clinical improvement. Which fraction of the protein is responsible for the skin necrosis is difficult to determine as all the globulin fractions and the albumin rose shortly before improvement commenced.

The dramatic improvement in the blood chemistry and the clinical state after steroid therapy indicate that this may be a hopeful line of treatment in this type of case.

TABLE I.

	(g. %).		
	Total.	Albumin.	Globulin.
28 : vi : 57	3.6 .	1.2 .	2.4 .
4 : vii : 57	2.1 .	1.2 .	1.9 .
17 : vii : 57	4.2 .	1.9 .	2.3 .
28 : viii : 57	3.9 .	1.7 .	2.2 .
18 : ix : 57	3.7 .	1.5 .	2.2 .
10 : x : 57	4.8 .	2.2 .	2.6 .
Prednisolone started.			
5 : xi : 57	5.4 .	2.8 .	2.6 .
4 : xii : 57	6.1 .	3.1 .	3.0 .
20 : ii : 58	6.0 .	2.2 .	3.8 .
16 : iv : 58	6.0 .	2.4 .	3.5 .
1 : v : 58	6.3 .	2.9 .	3.4 .

Reticulo-granuloma Eosinophilicum Cutis Simplex.—Dr. P. B. MUMFORD.

A boy aged 10.

In September 1955 the patient developed a single red nodule on the chin. A fortnight later a generalized eruption followed, the lesions being diffusely scattered over the buttocks, face and limbs. For the most part these were firm nodules varying in size from 0.3 to 1 mm. in diameter. Some were necrotic but none pustular. The mucous membranes were clear and there was no adenitis, but for 4 days a mild pyrexia without constitutional upset was noted. Irritation and tenderness were absent. Heavy dosage of cortisone was followed in 5 weeks by complete clearance.

Biopsy showed an eosinophilic granuloma. Skiagrams of chest, long bones, skull and spine were normal. A blood count was normal.

Since 1955 an occasional nodule appears on the limbs only. These do not necrose or disappear spontaneously, but invariably clear with a single exposure of 150 r x-ray. The present lesion is of 2 weeks' duration on the left calf.

Oil Granuloma (following penicillin injections).—Dr. CECIL W. MARSDEN.

A 62-year-old housewife.

A tender mass appeared on the right buttock 4 weeks after treatment in hospital in 1947 for retro-ileal appendicitis with abscess formation. It was symptomless until 4 months ago, when it became an indurated and discharging area with tenderness on pressure. The patient had received treatment in 1947 with injections of penicillin 100,000 units 8-hourly for a period of 5 days. This was probably the B.P. preparation of penicillin in beeswax and arachis oil.

The patient also complains of pain in the region of the lumbar spine which commenced 6 months ago, and has now disappeared, being replaced by pain in the right leg and paraesthesiae in the toes of the right foot.

On examination there is an indurated mass in the right buttock about 7 cm. in diameter. It is fixed to the overlying epidermis which presents an irregular surface of a dusky purple colour.

General physical examination shows no abnormality, and there are no abnormal neurological signs in the legs.

Investigations.—*Direct Microscopy*: Material from sinus (21 : ii : 58)—No mycelial filaments.

Histology (20 : iii : 58).—There is a granuloma occupying the whole thickness of the section. The epidermis is ulcerated at one point, the adjacent edges showing acanthosis and pseudo-epitheliomatous hyperplasia. The granuloma consists of lymphocytes and plasma cells surrounding clear rounded spaces (paraffin section). Between these spaces are foam cells and in the deeper layers fibrosis is present. Frozen sections stained with Sudan III show the clear spaces occupied by a deeply staining homogeneous material. Diagnosis—Oil granuloma.

Blood.—W.R. and Kahn negative.

Skiagram of lumbar spine normal.

Comment.—Cases of oil granuloma have been described following the injection, either accidental or therapeutic, of a wide variety of oily substances. Although mineral oils are the most frequent offenders, granulomas have also followed the injection of vegetable oils, in particular olive oil.

Experimental injections of oil in rats have shown that many different vegetable oils can cause granulomata, and the beeswax and peanut oil of penicillin injections have been reported as causing a cellulitis—presumably a foreign body reaction.

I can find no direct reference to the production of an oil granuloma by beeswax and arachis oil.

Granular Cell Myoblastoma.—Dr. J. G. COBURN.

A man aged 61.

Previous history and family history.—No skin disease.



FIG. 1.

History.—Twenty months ago he noticed a small lump on the back of the neck, which gradually enlarged. There was no pain or itching.

On examination.—A dome-shaped brownish-red tumour $\frac{3}{4}$ in. in diameter, of firm consistency and easily moved on the underlying tissues. There is a minute telangiectasis on the surface.

There is a small hard nodule in the skin of the right thigh. The skin is otherwise normal.

No enlargement of lymph nodes.

General examination.—Normal.

Histology.—There is irregular acanthosis of the epidermis, and almost the entire dermis is filled with large, pale cells having a granular cytoplasm and multiple nuclei. (Fig. 1).

The nodule on the right thigh was excised and showed the typical histology of a histiocytoma.

BOOK REVIEWS.

Dermatologia Venezolana is the first number of the official journal of the Venezuelan Society of Dermatology, Venereology and Leprology. The main paper is a study of cutaneous leishmaniasis in Venezuela, a disease that is increasing there, by Rafael Medina and Jesus Romero.

This paper was awarded the Martin Vegas prize for its excellence.

G. W. B.

GANS'S HISTOLOGY.*

THE publication of the second edition of Gans's work on the Histology of Diseases of the Skin, after an interval of thirty years, is particularly welcome and, in order to cope with such a monumental effort, Dr. Gans has been fortunate in enlisting the help of Dr. Gerd-Klaus Steigleder who, I gather, has contributed much in reviewing the vast literature that has accumulated during that long interval.

It is no easy matter to review such a comprehensive work which covers more than 1150 pages and contains over 550 illustrations, most of which are in colour. The second edition, like the first, still remains the most thorough and authentic work of its kind and is now brought up to date by alterations of the original text and by the addition of very numerous descriptions together with the incorporation of many new illustrations.

Among the many virtues of skin pathology is that material can be obtained very simply and studies made in various stages of the natural evolution of the disease and its response to treatment, and the authors have not failed to take full advantage of this. They have devoted a brief chapter to embryology of the skin and its appendages and another to changes in the cadaver. The latter is a subject of considerable interest and it is hoped that the authors may have the opportunity of enlarging on this subject, covering the pathological and histochemical changes which occur after death as a result of exposure to the sun etc., about which our present knowledge is very scanty despite its extreme importance to the student of forensic medicine.

The books are devoted to the pathology of the skin in the widest sense and a careful reading fails to reveal the omission of any disease, no matter how insignificant or rare. Their style leaves nothing to be desired and the illustrations, particularly those drawn in colour and black, are excellent guides to the subject. As good as many of the new microphotographs are they cannot be compared in value with the former, missing as they do many of the critical details; although the camera does not lie it does not give the complete picture of the changes as seen by the pathologist with his fingers on the fine adjustment of his microscope and which can only be portrayed faithfully by the expert artist.

A work of this kind could only be produced by the prodigious effort of such industrious and accredited authorities but they are indeed fortunate in having the

* *Histologie der Hautkrankheiten*. OSCAR GANS and GERD-KLAUS STEIGLEDER. Berlin, Göttingen, Heidelberg: Springer-Verlag. 2nd Edition. Vol. I (1955). *Normale Anatomie und Entwicklungsgeschichte, Leichenerscheinungen, Dermatopathien, Dermatitis—I*. Pp. 726, 258 illus., mostly coloured. Price DM. 285. Vol. II (1957). *Dermatitis—II, Örtlich Übertragbare Infektiöse Gewebsneubildungen, Tierische Parasiten und Fremdkörper, Störungen des Kreislaufs, Entwicklungsstörungen, Echte Geschwülste*. Pp. 706, 290 illus., mostly coloured. Price DM. 298.

support of Springer's who have permitted them to write so fully on their subject despite the almost prohibitive cost of the books. To say that these volumes are an essential to the library of every dermatologist would be misleading even if he were thoroughly acquainted with German; for this is a very detailed work covering the whole field. It would however prove invaluable to the skin pathologist and to the general pathologist who, thanks to the first edition of this work and others published before and since its issue, appear to be taking a more lively interest in this important branch of pathology.

The books are very well documented with the more important references to the literature—and this occupies a hundred and twenty-three pages—but whereas, in the earlier edition, these were inserted at the end of the relevant chapters, they are now more suitably placed at the end of each volume. The indices, to which the first volume devotes sixty-nine pages and the second, covering the subject matter of both volumes, a hundred and sixty pages, are excellent.

It would be superfluous to refer to the quality of the production of the books coming, as they do, from the internationally famed house of Springer who have maintained their exceptionally high standard.

I. M.

CURRENT LITERATURE.

ERYTHRODERMAS OF INFANCY: A DIFFERENTIAL CLINICAL STUDY. LESTER PAXTON BARKER, PAUL GROSS and JOHN T. MCCARTHY. (1958) *Arch. Derm. Syph., Chicago*, **77**, 201.

Ritter's disease is an acute bacterial infection which responds promptly to broad spectrum antibiotic therapy whereas Leiner's disease is due to vitamin deficiency and occurs mostly in breast fed infants whose mothers have a deficient diet. It responds to the administration of biotin, though coincident diarrhoea or systemic infection must be controlled. Seborrhoeic dermatitis of infancy may be related to Leiner's disease into which it sometimes progresses. J. K.

INTERMEDIARY METABOLISM OF PHENYLALANINE AND TYROSINE IN DIFFUSE COLLAGEN DISEASES: I. THE PRESENCE OF 2,5-DIHYDROXYPHENYLPYRUVIC ACID IN THE URINE OF PATIENTS WITH COLLAGEN DISEASE. NAGAO NISHIMURA, MASATAKA YASUI, HISASHI OKAMOTO, MINORU KANAZAWA, YAHITO KATAKE and YOKIO SHIBATA. (1958) *Arch. Derm. Syph., Chicago*, **77**, 255.

The authors found 2,5-dihydroxyphenylpyruvic acid constantly present in the urine of patients with diffuse collagen disorders and not present in other patients or in healthy subjects. They conclude that the block of the intermediary metabolism of phenylalanine and tyrosine at this metabolic stage to homogenistic acid is one of the most important aetiological factors of collagen disease. J. K.

EFFECTS OF ORAL METHOXSALEN (8-METHOXYPSORALEN) ON SUNBURN AND SUNTAN: A BLIND CLINICAL TRIAL. FARRINGTON DANIELS, JR., CARL E. HOPKINS and THOMAS B. FITZPATRICK. (1958) *Arch. Derm. Syph., Chicago*, **77**, 503.

Methoxsalen, a known potent photodynamic agent, has been used to treat vitiligo. The present investigation was undertaken to test its value in subjects who sunburnt easily and tanned poorly. There was no difference between the results in those given the drug and those given a placebo, in fact those who claimed problem sunburning reacted more to the placebo than to the drug. J. K.

TREATMENT OF WARTS WITH CANTHARIDIN. WILLIAM L. EPSTEIN and ALBERT M. KLIGMAN. (1958) *Arch. Derm. Syph., Chicago*, **77**, 508.

Cantharidin in a 0.7% solution in equal parts of acetone and collodion was used in 61 patients with warts. It was found especially useful in periungual warts, had merit in selected cases of ordinary and plantar warts but is not recommended for mosaic warts. Ordinarily a frank blister results and one application may be sufficient but the treatment can be repeated if necessary. Effectiveness is not dependent on clinical blistering. J. K.

SENSITIVITY TO FLUORESCENT (BLUE-GREEN) LIGHT. JOHN H. LAMB, PHYLLIS E. JONES, GERBERT REBELL and HERMAN D. ALSTON. (1958) *Arch. Derm. Syph., Chicago*, **77**, 519.

Certain cases of polymorphic light eruptions that do not seem to improve with anti-malarial drugs may be due to sensitiveness to blue-green light. The authors report 6 cases of light sensitive eruption due to fluorescent lighting. Treatment was removal from proximity to fluorescent tubes, screening with frosted glass and parenteral use of testosterone propionate. J. K.

RING DERMATITIS: PRIMARY IRRITATION FROM THE ACTION OF SALT ON JEWELRY ALLOYS. L. EDWARD GAUL. (1958) *Arch. Derm. Syph., Chicago*, **77**, 526.

Patch tests with metals may be negative even where a clinical diagnosis of metal dermatitis seems obvious. It would appear that some at least of these cases can be explained by the production of a primary irritant by the action of an adequate concentration of salt on copper or copper alloy in silver jewelry. J. K.

VASCULAR REACTIONS IN CHRONICALLY INFLAMED SKIN. WILLIAM S. REED, ROBERT R. KIERLAND and CHARLES F. CODE. (1958).

I. MECHANICAL STIMULI IN THE SKIN: INHIBITION OF WHITE DERMOGRAPHISM. *Arch. Derm. Syph., Chicago, 77, 91.*

II. ACTION OF EPINEPHRINE AND PHENTOLAMINE: ACTION OF ACETYLCHOLINE AND METHACHOLINE, AND THE "DELAYED BLANCH". *Arch. Derm. Syph., Chicago, 77, 181.*

III. ACTION OF HISTAMINE, THE HISTAMINE RELEASER 48-80, AND MONOETHANOLAMINE NICOTINATE. *Arch. Derm. Syph., Chicago, 77, 263.*

All the experiments reported were carried out on patients suffering for the most part from atopic dermatitis, disseminated neurodermatitis, psoriatic erythrodermia and mycosis fungoides.

The first paper describes the white dermographism produced by stroking firmly such inflamed skins. It depends on mechanical stimulation of the skin and is independent of any chemical or neural stimulus; it is found only in the chronically inflamed skin and does not occur in acute conditions.

In the second paper the delayed blanching of the skin in atopic dermatitis is described. It does not occur in every patient but when present can be used to differentiate this disease from similar inflammatory disorders in which the normal red reaction occurs. This delayed blanch can be inhibited by the injection of atropine but not by phentolamine, diphenhydramine or procaine.

In the third paper the flare response to histamine is shown to depend on the acuteness of the inflammation present. The size of the wheal was reduced in more acute conditions but was more normal in chronically inflamed and slightly erythematous skin. The flare after an injection of histamine in patients who had white dermographism could be reduced or abolished by rubbing the skin before or after the injection. The potent histamine releaser 48-80 (condensation product of *p*-methoxyphenylethyl-methylamine and formaldehyde) had a similar effect.

Monoethanolamine nicotinate which has nicotinic acid activity does not produce a delayed blanch when injected intradermally. J. K.

PUSTULAR PSORIASIS. JOHN T. INGRAM. (1958) *Arch. Derm. Syph., Chicago, 77, 314.*

The author considers acrodermatitis continua or perstans, pustular bacterid and pustular psoriasis are perhaps only variants of one distinctive clinical entity, and as they occur 4 times more frequently in psoriatic patients than in others he groups them all under the term pustular psoriasis. They are considered to be combined eczematous and psoriatic reactions which explains their stubbornness.

Treatment by other than local applications (tar and ichthammol-like preparations) is not beneficial. J. K.

ALKALINE PHOSPHATASE IN ALOPECIA AREATA. ALFRED W. KOPF and NORMAN ORENTREICH. (1957) *Arch. Derm. Syph. Chicago, 76, 288.*

Alkaline phosphatase activity in affected hair follicles is diminished or absent during the early stage of alopecia areata but is restored in later stages. J. K.

THE NEUROHISTOLOGY AND NEUROPHYSIOLOGY OF THE ITCH SENSATION IN MAN.

WALTER B. SHELLEY and ROBERT P. ARTHUR. (1957) *Arch. Derm. Syph., Chicago, 76, 296.*

This lengthy article (27 pages) gives the results of the authors' study of the relevant literature and experiments in the production of itch in man. Itch is produced by a variety of stimuli and the sensation travels at the comparatively slow rate of 2 metres per second along the fine unmyelinated C fibres of the peripheral nerves which also carry "burning pain" sensation. The itch point is a rich aggregate of fine fibres in the sub-epidermal area and itch is commonly produced by proteinases (endopeptidases) acting on these nerve endings. Great differences were found in itch sensitivity in different individuals and in different areas of the body. J. K.

TYROSINASE IN THE EPIDERMAL MELANOCYTES OF WHITE HUMAN SKIN. GEORGE SZABÓ. (1957) *Arch. Derm. Syph., Chicago, 76, 324.*

Failure in the past to demonstrate the presence of tyrosinase in melanocytes of mammalian skin has been due to technical imperfections especially the presence of too much dermis in the specimen. If the epidermis is separated from the corium before being treated with tyrosine and viewed from the dermal side, melanin granules will be seen in the melanocytes indicating the

presence of tyrosinase to produce the necessary reaction. A comparison between dopa positive and tyrosine positive cells shows that the number is usually the same but this varies in different regions of the body. J. K.

EXAMINATION OF NORMAL AND MYXOEDEMATOUS SKIN: USE OF MOWRY'S ALCIAN BLUE—PERIODIC ACID-SCHIFF TECHNIQUE. EDWARD P. CAWLEY, CHARLES H. LUPTON, CLAYTON E. WHEELER and J. F. A. McMANUS. (1957) *Arch. Derm. Syph., Chicago*, **76**, 537.

This combination of stains enables one to differentiate between acid mucopolysaccharides, which stain various shades of blue, and 1, 2-glycols, which take on a magenta hue. It is shown that acid mucopolysaccharides probably take part in the process of keratinization, sweat secretion and hair growth and that the mucinous accumulations found in the skin in true myxoedema circumscribed myxoedema and lichen myxomatousus are rich in acid mucopolysaccharides.

J. K.

AN APPRAISAL OF THE THERAPEUTIC EFFECT OF RIBOFLAVIN IN PSORIASIS. ASHTON L. WELSH and MITCHELL EDE. (1957) *Arch. Derm. Syph., Chicago*, **76**, 595.

Riboflavin administered by the mouth or parenterally, in moderate or in massive dosages to 348 patients with psoriasis failed to produce any significant response. J. K.

HISTAMINE LEVELS IN HUMAN SKIN. HERBERT H. JOHNSON. (1957) *Arch. Derm. Syph., Chicago*, **76**, 726.

Marked variations in histamine levels occurred in different regions of the body. The levels varied from over 30 μg . of histamine base per gram of skin in upper eyelids and lip, with decreasing levels in submental triangle, scalp, infraclavicular region, lower abdomen to 6.6 μg . per gram in the skin over the xiphoid cartilage. J. K.

POISON IVY (RHUS) DERMATITIS: AN EXPERIMENTAL STUDY. ALBERT M. KLIGMAN. (1958) *Arch. Derm. Syph., Chicago*, **77**, 149.

This article summarizes our knowledge of rhus dermatitis; there are 105 references. In poison ivy are four antigenic compounds, catechols with a 15 carbon atom side chain in the 3 position, that differ only in the degree of unsaturation of the side chain. The antigen in Japanese lacquer differs only in the position of one of the unsaturated bonds.

In the U.S.A. about half the population is sensitive to poison ivy, the proportion being higher in the white than the dark-skinned races. Sensitivity tends to decrease after the age of 60.

There is no adequate method of local protection of the skin or of desensitization. Local treatment by ordinary bland remedies is as effective as any other, including the use of steroid compounds, but systemic administration of a corticosteroid is beneficial. J. K.

GRANULOMATOUS CHEILITIS OF MIESCHER WITH CUTANEOUS MANIFESTATIONS RECAL-LING LUPUS ERYTHEMATOSUS. X. VILANOVA, J. PINOL AGUADE and C. CARDENAL. (1958) *Ann. Derm. Syph. Paris*, **85**, 278.

A boy of 14 had a granulomatous cheilitis of 4 years' duration accompanied by scaling red and atrophic lesions on the backs of the hands, fingers and the face. These suggested lupus erythema-tosus, but the authors believe that they were really manifestations of the same condition that was affecting the lips. Thus the concept of Miescher's disease must be extended beyond the region of the face. F. F. H.

GENERALIZED MICROPAPULAR DERMATOSIS WITH RETICULO-FIBROCYTIC STRUCTURE. ST. GH. NICOLAU and L. BALUS. (1958) *Ann. Derm. Syph. Paris*, **85**, 146.

The authors describe a dermatosis characterized clinically by a nearly generalized monomorphic eruption, formed at first by discrete micropapular elements; these later run together forming diffuse almost sclerodermatous plaques. The lesions of the central part of the face give a peculiar and characteristic appearance. Histologically the papular lesion is formed of a proliferation of reticular cells with an evident tendency to develop along fibrocytic lines, accompanied by a sclerohyaline reaction of the connective tissue stroma. They believe the condition to be a benign reticulosis. F. F. H.

PORPHYRINURIA AND DIURESIS IN THE QUIET PERIOD AND DURING EXACERBATIONS OF CONGENITAL PORPHYRIA. F. OTTOLENGHI-Lodigiani. (1957) *Giorn. ital. Derm.*, **98**, 601.

On one patient 75 consecutive daily observations of the volume of urine and its porphyrin content were made. Clinical exacerbations of the disease recurred at regular intervals of 12-13 days, each preceded by a decrease of the quantity of porphyrin excreted in the urine and each accompanied by a sudden increase in its excretion. There is a less clearly defined tendency for a reduction in volume of urine to precede the exacerbation. Readers should note that the first graph (of the results over the whole period) does not entirely correspond with the data in Table I. The author fails to stress the most remarkable periodicity of the exacerbations, which fell on days 6, 18, 31, 43 and 68; nor does he make the point that on days 56 and 57, a time when an exacerbation could have been predicted but failed to develop clinically, the excretion of porphyrins rose to about the same extent as it did during the manifest exacerbations. A. L.

OBSERVATIONS ON THE HISTOCHEMICAL DISTRIBUTION OF ALKALINE PHOSPHATASE IN THE SKIN. G. FARRIS. (1957) *Giorn. ital. Derm.*, **98**, 611.

In the guinea-pig the main sites were the epidermis (subcorneal) and pilosebaceous apparatus, and in the human the blood vessels and sweat glands (secretory portion). A. L.

THE RELATIONSHIP BETWEEN MELANOGENESIS AND OTHER SIMILAR BIOCHEMICAL PROCESSES. S. SACCHI. (1957) *Giorn. ital. Derm.*, **98**, 635.

A biochemical essay on the cyclic amino acids whose metabolism produces brownish-black pigments, leads to speculation about the melanins having alternative modes of origin. A. L.

CLINICO-BIOLOGICAL OBSERVATIONS ON NECROBIOSIS LIPOIDICA. L. DATOVO. (1957) *Giorn. ital. Derm.*, **98**, 654.

One patient presented granuloma annulare and discoid atrophic patches, and the other plaques which ulcerated. Both were poorly controlled diabetics and in both the lesions healed on a regime of insulin plus lipotropic substances (lipoeaic and amino acids). Both cases had a reversal of the albumen/globulin ratio, in the first case the alpha-two globulins were increased, and in the second the gamma globulins. The histopathology of all the lesions was uniform in distinction to the diverse clinical features. Vascular lesions were prominent, and the author regards the disease as part of the vascular damage that accompanies diabetes mellitus. A. L.

BLEPHARO-CILIARY LOCALIZATION OF TRICHOPHYTON ROSACEUM. M. P. BONANNI. (1957) *Giorn. ital. Derm.*, **98**, 667.

The boy, who had tinea circinata and scalp ringworm with pustulation, developed an inflammation of the left upper eyelid, whose eyelashes broke off. The fungus was grown from crusts and eyelashes. A. L.

ACUTE VASCULAR PURPURA FOLLOWING IMMUNIZATION WITH ASIATIC INFLUENZA VACCINE. M. STEFANINI, S. PIOMELLI, R. MELE, J. T. OSTROSKI and W. P. COLPOYS. (1958) *New Engl. J. Med.*, **259**, 9.

A widespread and severe purpuric eruption appeared in a woman 7 days after she had been given 2 ml. of polyvalent Asiatic influenza vaccine. The eruption was attributed to an allergic reaction, the virus itself probably being the allergen. No sensitivity was found to egg protein or the preservative used. Passive transfer of sensitivity was carried out successfully. A. D. P.

TREATMENT OF EARLY SYPHILIS WITH PENICILLIN. R. R. WILLCOX, F. J. G. JEFFERISS and G. L. M. McELLIGOTT. (1958) *Brit. J. vener. Dis.*, **34**, 14.

The results of the treatment of 864 cases of primary and secondary syphilis at St. Mary's Hospital, London, are reviewed. Of these, 561 received treatment with penicillin and a short course of arsenic and bismuth, 183 were given penicillin and a maximum of 10 injections of bismuth, and 120 received penicillin alone. In the series, as a whole, the clinical and serological results have been excellent and seem, if anything, to have been better, rather than worse, when penicillin alone was used. The authors conclude that penicillin alone can be confidently recommended as the treatment of choice in early syphilis. W. G. A.



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